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EVALUATION OF DIS-LUBTOUT, A NEW CO-PROCESSED TABLETING EXCIPIENT 3. PHYSICO-CHEMICAL PROPERTIES OF WET GRANULATION ASPIRIN TABLETS LUBRICATED WITH DIS-LUB-TOUT

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Abstract

Dis-Lub-Tout, a newly co-processed bi-functional tableting excipient was evaluated against magnesium stearate, MS, for its lubricant property and in a model wet granulation ASA tablet system prepared with lactose as tabletted based material. Dis- Lub-Tout increased the flow rate and negatively affected the densification behavior of the tested formulations. It accelerated the disintegration and dissolution rates of the tested tablets which were functions of the concentration of the lubricant in the tested tablets. Thermo-degradation study showed that the decomposition of ASA in tablets lubricated with Dis-Lub-Tout followed the pseudo first order pattern with slower rates which were amenable to Arrhenius treatment. ASA degradation rate constants in tablets stored under humid conditions was faster.

Keywords: Lubricant property of Dis-Lub-Tout, Powder densification, Disintegration and dissolution of tablets, ASA decomposition in tablets

1 . Introduction

Excipients are chemically and therapeutically inactive substances used to formulate dosage forms and perform different functionalities including drug delivery system during manufacture and enhance stability, bioavailability, overall safety and effectiveness of the drug delivery system during storage or use and patient acceptability (Villanova , Ayres, & Oréfice, 2011). The discovery and development of excipients of improved functionality and developing new grades of existing materials are costly, tedious and need comprehensive laboratory work and detailed clinical trials which are time consuming and economically expensive (Philip, et al, 2010).

A great deal of attention was directed to co-processing or particle engineering technique as a means to develop new in-expensive excipients of desired multi-functional activities in short time. Co-processing technique is simply defined as admixing of two or more existing excipients at sub-particle level to produce new excipients of substantial benefits of the incorporated excipients and minimize their drawbacks (Gohel & Jogani, 2003).

Lubricants are essential additives in tablet and capsule formulations. They reduce inter-particle friction and enhance powder flow during tablet making and capsules filling. They are traditionally evaluated by measuring their effects on the flowability properties and consolidation behaviors of powder formulations (Hoag, Dave, Moolchandani 2008; Esezob, 1991), the tensile strength, friability, disintegration and dissolution behaviors of the finished compacts. Lubricants processed from edible vegetable oils showed better performance than magnesium stearate, MS, in terms of imparting no adverse effects on the properties of the finished tablets (Esezob, 1991; Onyechi, Udeala, 1990).

Wet granulation, the old and classical tabletting is still the technique of choice to produce tablets whenever direct compression technique failed to apply. Freely flowing granules of enhanced compressional behaviours and tablets of enhanced physico-chemical properties are usually produced by wet granulation.

The chemical nature and composition as well as the concentration, C, of lubricants used in ASA tablets play a vital role in the chemical instability of the tablets.

MS and stearic acid were reported to accelerated the chemical decomposition of aspirin in tablets.

The objectives of this work was to evaluate the lubrication effects of Dis-Lub-Tout on the flow and densification properties of lactose granules and on the physico-chemical properties of the corresponding ASA tablets.

2. Materials and methods

2.1. Materials

A sample of Dis-Lub-Tout powder supplied from this laboratory was used as given. Lactose monohydrate and gelatin powders were given by LOBA Chemie Ltd., Mumbai- 400005, India. HCl (37.5%), ASA were purchased from Scharalab, S.L., Gato Prez, Spain.

2.2. Methods

2.2.1. Lactose granulation

A 500 g sample of lactose powder was passed through a 90 μm stainless steel sieve mesh and dried at 45^{o} C for 2 h using a laboratory Binder dryer. The powder was then kneaded with 5 w % gelatin using a laboratory

porcelain mortar. The wet mass was dried at 40^{o} C for 2 h and then forced through a 1.4 mm stainless sieve mesh. The resulted large granules were further dried at 40^{O} C and passed through a 125 um stainless steel sieve mesh. The produced granules were equilibrated at room condition for 24 hours and kept in screw capped powder bottles till use.

2.2.2. Evaluation of lactose granules, LG

The produced granules were evaluated for the effective mean granule diameter, size distribution and percent of fines. For the test, a 100 g granules sample was placed on the top sieve of a set of stainless steel sieves (Fritsch, GmbH, FRG) arranged in a descending order. The sieve set was tightly covered and shaken for 20 min. using a magnetic shaker. The weight of the granules fractions retained on the sieves were precisely determined and employed to calculate the effective mean granules diameter. The granules fraction passed through 63 μm sieve mesh was precisely weighed and employed to calculate percent of fines. The granules fraction of 125 μm mean granule diameter was employed to carry out all the tests. The moisture content (weight dry basis) was determined as mentioned earlier (Aly 2006). The flow rate, repose angle, and porosities (inter and intra-granular) of the prepared LG were determined.

2.2.3. Densities and specific surface area, SA, determination

The liquid displacement technique using distilled water as a non-dissolving liquid and a 25 ml pycnometer calibrated at room temperature were employed to determine the apparent density of given samples of LG and aspirin. The mean of such five determinations was calculated as the apparent density of the given sample. Bulk and tap densities and packing fraction of LG were determined as mentioned earlier (Aly 2006).

Adsorption and air permeability methods are usually employed to measure

SA of LG. In this laboratory SA was calculated as follows: It was assumed that LG are symmetrically spherical and its diameter is d. The surface area, A, of a granule is given by:

$$A = \pi d^2 \qquad \text{Eq.1}$$

The number, N, of LG in one gram is given by:

$$N = 6 / \pi d^3 \rho. \qquad \text{Eq.2}$$

Multiplying Eq.1 by Eq. 2 , one may simply calculate SA as:

$$SA = N.A = 6 / d \rho \qquad \text{Eq.3}$$

2.2.3.3. Flow rate and repose angles LG

The early prescribed funnel technique (Aly 2006) was employed to determine the flow rate and repose angle of LG. The effects of increasing

concentrations of a given lubricant on the flow rate and repose angles were also studied.

2.2.4. Formulation, compression and evaluation of aspirin tablets

The received aspirin powder was pulverized using a porcelain mortar and passed through 125 µm sieve mesh. This powder fraction was used to formulate the tablets. Simple mixing technique was employed to prepare aspirin /LG powder mixtures containing 33wt % aspirin using a locally assembled drum mixer of suitable capacity. The prepared mixture was subjected to the uniformity of content test and the obtained result was satisfactory (98.34 % ± 0.18 w/w). The mixtures were lubricated with increasing concentrations of a given lubricant using the locally assembled mixer. Lubrication process was carried out for 5 min. The lubricated batches were compressed into tablets using a single punch tabletting machine (F 3 single punch machine, Manesty, UK) The machine was used to compress tablets of 300 mg mean weight, 9 ±0.1 mm mean diameter and of 6 ± 0.5 kg mean crushing strength, *h*, containing 100 mg aspirin from un-lubricated powder batch. The machine was stopped whenever it was necessary to clean the punches from the sticky powder. The machine settings were kept constant throughout compressing batches lubricated with Dis-Lub-Tout or MS.

2.2.5. Evaluation of a lubricant material

The de-compactibility, k_c , and de-compressibility, k_r , indexes of a given LG batch lubricated with C of a respective lubricant were calculated from the slopes of the relations:

$$h = h^o \, Exp. \, k_r \, . \, C \qquad \text{Eq.1}$$

and

$$\varepsilon = \varepsilon^o \, Exp. \, k_r \, . \, C \qquad \text{Eq.2}$$

where h^o and ε^o stand for the crushing strength and porosity of the un-lubricated aspirin tablets, respectively. Moreover, the effects lubricants on the disintegration and dissolution rates of the tested tablets were assessed.

2.2.6. Disintegration and dissolution rate determination of tablets

The disintegration of aspirin tablets in 0.1N HCL was carried out following BP 2010 A USP disintegration test apparatus (Erweka Appratabeau, Darmstadt, FRG) in 0.1 HCl The effect of a given lubricant on the disintegration rate constant of a given tablet batch was determined.

A rotating basket USP dissolution rate test apparatus (DT-D Erweka, FRG) was employed to study the dissolution profiles of a given tablet batch in 0.1N HCl maintained at 37± 0.5^o C. The apparatus was monitored at 100 ± 5 rpm. All the USP requirements for the dissolution rate test were kept

constants. Aspirin liberated in a withdrawn sample was determined spectrophotometrically at 270 nm with a reference to a calibration curve constructed using a pure aspirin sample as used in formulation.

2.2.7. Study of Moisture sorption isotherm of aspirin tablets

A sample of 10 tablets randomly collected from the batch lubricated with 3 wt% was stored on shelf at 40^o C-RH 75% using a Gallenkamp humidity oven (Gallenkamp, UK) . At a predetermined time interval, the stored tablets were examined for the amount of adsorbed moisture and for the changes on the physical properties caused by the adsorbed moisture.

2.2.8. Accelerated stability testing of aspirin tablets

2.2.8.1. Thermo-degradation study

Aspirin tablet batches lubricated with 3 wt% of Dis-Lub-Tout or MS was stored at 40, 50, 60^o C. At a predetermined time interval, the percent aspirin remained intact in a stored batch was determined. The physical properties of the tablets were also re-assessed.

2.2.8.2. Degradation involving moisture

The batches lubricated with 3 wt% of Dis-Lub-Tout or MS were also stored at 50^o C- RH 47% , 40^O C-RH 75% and on shelf (35 ± 2^o C- RH 43 ±2%). At a predetermined the percent aspirin remained intact was determined. The physical properties of the tablets were also re-assessed.

3. RESULTS

3.1. LG physical properties

Table I shows some physical properties determined for aspirin powder and LG. Fig.1 shows that at equal levels of concentrations, Dis-Lub-Tout and MS almost equal positive effects on the flow rate of the tested LG. They decreased the repose angle to levels parallel to the increase in the flow rate.

3.1.4. Physical properties of aspirin tablets

Table 2 shows that aspirin tablets were uniform in weight and thickness according to specifications of BP 2010. Lubrication did not show a significant effect on the uniformity of the examined tablets. Figs.2 (a,b) show that h of the tested tablets decreased while ε increased, respectively. Figs.3 (a,b) show that Dis-Lub-Tout accelerated the disintegration dissolution rates the tested tablets.

3.1.4. Moisture sorption exhibited by aspirin tablets

Table 3 shows that tablets lubricated with Dis-Lub-Tout adsorb moisture more than the tablets lubricated with MS.

3.1.5. Degradation of aspirin tablets

Figs.4 (a,b) shows the first order degradation pattern of the tested aspirin tablets. The degradation of aspirin in tablets lubricated with MS was higher. The decomposition rate constants, k_t, of the tested tablet batches were amenable to Arrhenius treatment as shown in Fig.4b. The activation energy, ΔE, and the frequency factor, A, calculated from the plot are given in Table 3. Moisture accelerated the decomposition of ASA tablets as shown in Fig. 5. The effects of moisture sorption on *h* and volume of the tablets are given in Table 3. Little changes were recorded for the tablets lubricated with MS

4. DISCUSSION

The produced LG were freely flowing. The addition of a lubricant to LG reduced the inter-granules fiction forces and facilitating the granules slippage and movement and therefore the flow rate increased and repose angles decreased, respectively. Due to the granules isolation by a film layer of the added lubricant, the compressibility decreased and the porosity of the corresponding tablets increased, respectively. The curves seen in Fig.2 were lacking for linearity which is due to the mixed deformation mechanism (plastic and brittle) of lactose. This agrees with the early reported result (Bolhuis & Holzer, 1996). The de-compressibility index, k_r, of the tested granules was calculated from the straight line segment of the curve in Fig. 2 and the data given in Table 2 show that Dis-Lub-Tout generated higher k_r values. The calculated de-compactibility indexes, k_p , for the granules lubricated with Dis-Lub-Tout and MS are also given in Table 2. The tested lubricants had the same effect on LG compactibility. It is seen in Figs. 3(a, b) that Dis-Lub-Tout showed a disintegration activity. It accelerated the dissolution of the tested tablets. This is expected since it is processed from regenerated cellulose which is a powerful disintegrant (Aly 2012; Leskinen 2003). It is also expected that this lubricant adorb moisture due to its cellulosic nature.

The thermo-degradation of ASA in the tested tablets followed the pseudo first order mechanism with rate constants amenable to Arrhenius treatment as seen in Figs. 5 (a &b). High temperatures accelerate ASA cleavage. In addition, heat and moisture had synergetic cleavage effect on ASA. ΔE and A values obtained for batches lubricated with Dis-Lub-Tout and MS were - 12.6, - 4.9 and 2.5×10^{-4} and $2,8 \times 10^{-15}$, respectively.

Tablet lubricated with MS and stored under humid condition exhibited less moisture sorption and therefore the changes in tablets physical properties due to moisture sorption were less.

CONCLUSION

Dis-Lub-Tout, succeeded as a lubricant and a disintegrant in a wet granulation tablet system prepared with lactose as granulated based material. It contributed to produce ASA tablets of enhanced phsico-chemical properties.

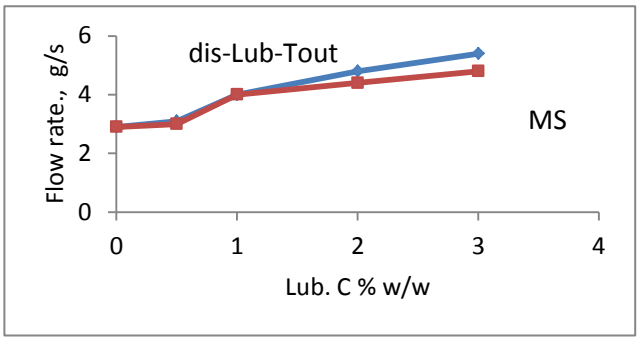
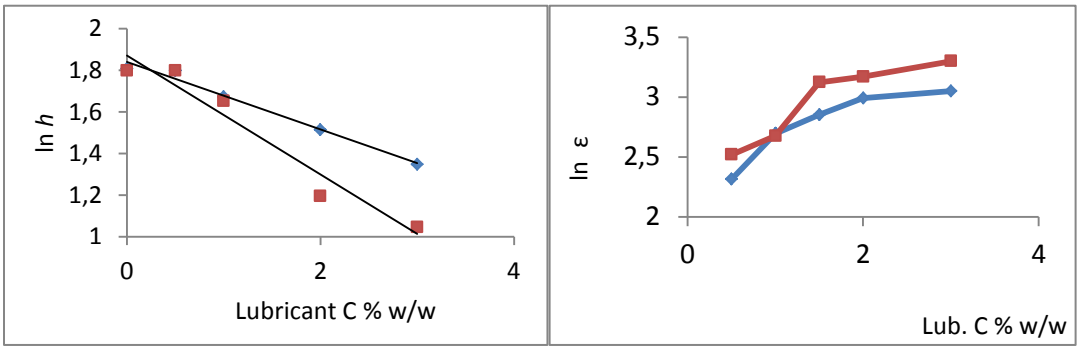


Fig. 1 Effect of lubricants on the flow properties of LG



Figs.2 (a,b)Semi-log plots of ε and *h* vs lubricant C for lablets compressed from LG

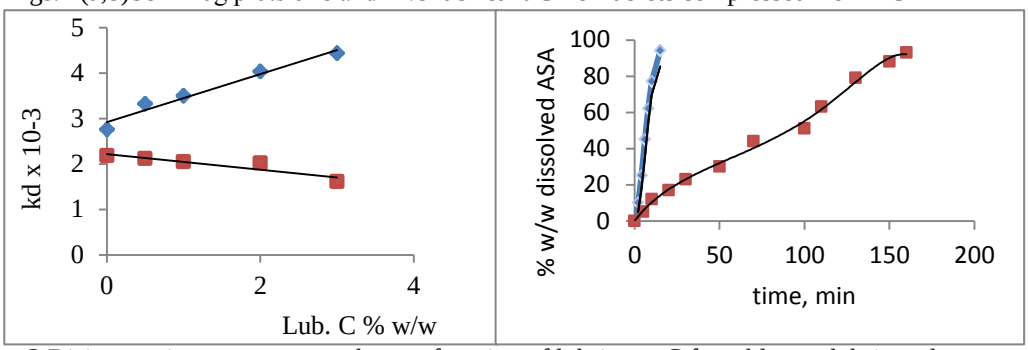


Fig. 3 Disintegration rate constant, k_d as a function of lubricant C for tablets lubricated with 3% a given lubricant. and the dissolution profiles of the tablets

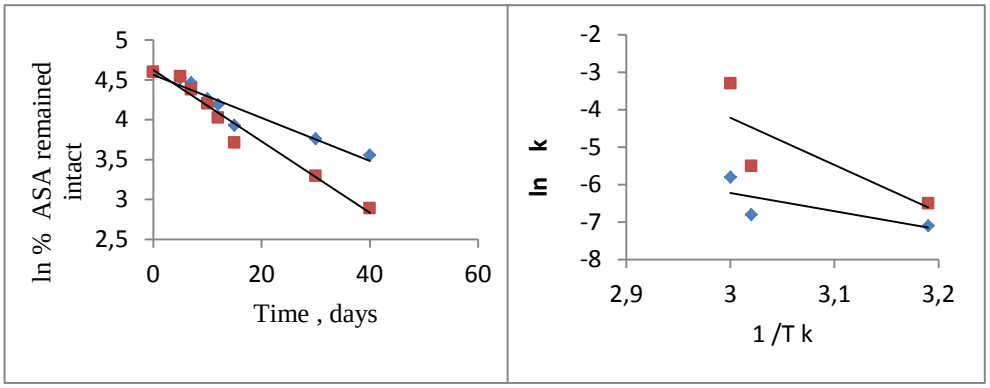


Fig.4 Thermo-degradation of ASA in tablets stored at 50°C and Arrehnius plot for the tested tablets.

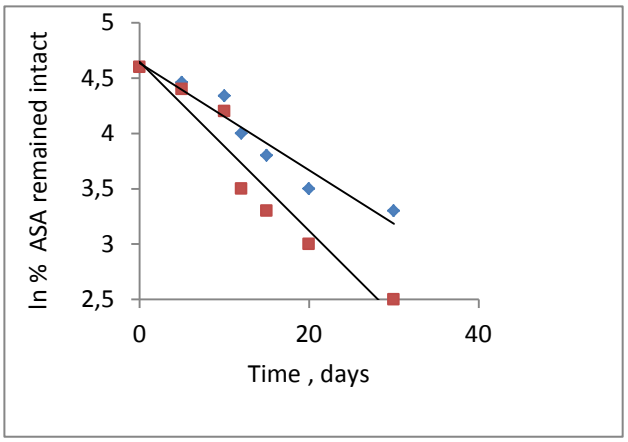


Fig.5 Degradation of ASA in tablets stored at 40° C -75% RH

Table I Physical properties of aspirin powder and lactose granules, LG.

Mat-erial tested	Mean part. diam., µm	Flow rate g/cc	Repose angle, degree	Moist. cont. %w/w	Specif. surf. area, m^2	Density g/cc true	bulk	tap	Porosity % Inter	intra	% pack fract of fines % w/w	
ASA	≤ 125	0.70	38	----	.0350	1.65	---	---	---	--	--	--
LG		95.2	29	3.50		1.58	0.68	0.69	13	24	16	43
	≥ 125				003.0							

Table 2 Some physical properties of ASA tablets lubricated with Dis-Lub-Tout and MS

Lub. C % w/w	Weight (g) Mean	C.V. %	Thickness (cm) Mean	C.V. %	Friability, F, (Loss% w/w) Mean	C.V. %
			Dis-Lub-Tout			
0.0	0. 2911	4.13	0.287	1.03	0.11	11.50
0.5	0.3010	1.19	0.310	1.03	0.13	10.20
1.0	0.3220	2.13	0.300	3.20	0.11	11.11
2.0	0.3322	3.17	0.318	2.29	0.15	9.05
3.0	0.3373	5.12	0.316	1.15	0.21	3.98
				MS		
0.0	0.2911	16.32	0.277	2.11	0.19	25.81
0.5	0.3010	21.51	0.280	1.81	0.15	13.15
1.0	0.3081	13.50	0.283	4.53	0.17	11.15
2.0	0.3152	3.81	0.286	2.72	0.18	16.22
3.0	0.3185	5.11	0.293	2.15	0.23	3.98

Table 3. Effect of sorbed moisture on volume and *h* for tablets lubricated with 3% w/w of the named lubricant an stored at 40o C-RH 75%.

Lubricant used	% w/w moist sorbed	% increase in tablet vol	% decrease in *h*
Dis-Lub-Tout	22	27	40
MS	14	12	23

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